

Amendments to the Specification:

Please replace the paragraph beginning at page 7, line 18 as with the following amended paragraph:

Figure 15 A is a bar graph which shows a comparison of RHAMM expression at a cell surface. Figure 15B provides the sequence of various RHAMM peptides (SEQ ID [[Nos.]] NOs: 14-20).

Please replace the paragraph beginning at page 8, line 20 as with the following amended paragraph:

Figures 26A, 26B and 26C illustrate that HA binding peptides (SEQ ID [[Nos.]] NOs: 28,56-58) including artificial mimics are able to block cell motility.

Please replace the paragraph beginning at page 9, line 1 as with the following amended paragraph:

Figure 27 is a bar graph which shows that treatment of injured cells with P-peptide (CSTMMSRSHKTRSHHV – ~~Seq. ID. No.~~ SEQ ID NO: 26) inhibits migration of HFF cells.

Please replace the paragraph beginning at page 9, line 3 as with the following amended paragraph:

Figure 28 is a bar graph which shows velocity of cells after addition of peptide ~~aa423-432 (Sequence ID No. 24)~~ amino acid residues 423-432 (SEQ ID NO: 24).

Please replace the paragraph beginning at page 11, line 9 as with the following amended paragraph:

Figure 50 depicts the human and murine sequence of RHAMM (SEQ ID [[Nos.]]NOs: 47 and 48 respectively).

Please replace the paragraph beginning at page 19, line 9 as with the following amended paragraph:

For example, within one aspect of the invention methods of identifying a peptide or polypeptide composition for treating a tissue disorder associated with a response-to-injury process, or, the proliferation of cells in a mammal is provided, comprising the general steps of: (a) selecting a sequence from a database screened for sequences comprising a peptide of the sequence BX7B (SEQ ID NO:28) wherein B is a basic amino acid, and X7 is a sequence of about seven residues is selected from any amino acid other than an acidic amino acid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, (b) preparing a composition comprised of the selected sequence; and (c) testing the prepared composition for the ability to inhibit podosome formation. Within certain embodiments, the peptide in (a) does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPVVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPVVR, or HREARSGKYK (SEQ ID [[Nos.]]NOs: 29-44 respectively).

Please replace the paragraph beginning at page 20, line 15 as with the following amended paragraph:

In still another aspect, the invention provides methods for detecting hyalauronic acid in a sample comprising the steps of: (a) incubating the sample with a hyalauronic acid binding peptide comprising a sequence selected from the group consisting of SEQ[[.]] ID NO: 1-10 and SEQ ID NOs: 71, 73 [[TO]]to 77 and (b) detecting an amount of a complex formed

between hyalauronic acid and the hyalauronic acid binding peptide. In one embodiment, the detecting employs an antibody that specifically binds to the hyalauronic acid binding peptide.

Please replace the paragraph beginning at page 20, line 22 as with the following amended paragraph:

In a related aspect, the invention provides methods of detecting a molecule that binds to a RHAMM polypeptide in a sample comprising the steps of (a) incubating the sample with the RHAMM polypeptide and with a RHAMM-binding polypeptide comprised of SEQ[[.]] ID NO: 21; and (b) detecting an amount of a complex formed between the sample and the RHAMM polypeptide by scoring for reduced binding between the RHAMM polypeptide and the RHAMM-binding polypeptide. In one embodiment, this method includes detecting which employs an antibody that specifically binds to the RHAMM-binding polypeptide.

Please replace the paragraph beginning at page 21, line 3 as with the following amended paragraph:

In another aspect of the invention, methods of identifying a peptide or polypeptide composition for treating a tissue disorder associated with a response-to-injury process, or, the proliferation of cells in a mammal is provided, comprising the general steps of: (a) selecting a sequence from a database screened for sequences comprising a peptide of the sequence SEQ ID [[Nos]]NOs: 73 to 77; (b) preparing a composition comprised of the selected sequence; and (c) testing the prepared composition for the ability to inhibit podosome formation.

Please replace the paragraph beginning at page 21, line 10 as with the following amended paragraph:

In a related aspect, the invention provides methods of detecting a molecule that binds to a RHAMM polypeptide in a sample comprising the steps of (a) incubating the sample with the RHAMM polypeptide and with a RHAMM-binding polypeptide comprising antibodies to of SEQ[[.]] ID [[Nos.]]NOs: 73 to 77; and (b) detecting an amount of a complex formed

between the sample and the RHAMM polypeptide by scoring for reduced binding between the RHAMM polypeptide and the RHAMM-binding polypeptide. In one embodiment, this method includes detecting which employs an antibody that specifically binds to the RHAMM-binding polypeptide.

Please replace the paragraph beginning at page 23, line 15 as with the following amended paragraph:

Numerous peptide mimetics may also be utilized within the present invention, including for example peptides such as:

SEQ[[.]] ID[[.]] NO: 1 (H4-5)B3;

SEQ[[.]] ID[[.]] NO: 2 (H4-5)BXBBXB;

SEQ[[.]] ID[[.]] NO: 3 (H4-5)BXBXBBB;

SEQ[[.]] ID[[.]] NO: 4 (H4-5)BXBBB; and

SEQ[[.]] ID[[.]] NO: 5 (H4-5)BXBB

where B is either lysine (K) or arginine (R) and X is a hydrophobic or neutral amino acid (*i.e.*, L, V, Q, S) and H represents a series of amino acids such that an alpha helix is formed, as determined by NN-predict EMBL protein analysis. This need not be an amphipathic or coiled coil helix but such would also be suitable. Specific examples of sequences fitting these motifs that have been analyzed for effectiveness on podosome include the following:

SEQ[[.]] ID[[.]] NO: 6 MMTVLKR;

SEQ[[.]] ID[[.]] NO: 7 MMTVLKVKRLR;

SEQ[[.]] ID[[.]] NO: 8 MMTVLKVKVKRK;

SEQ[[.]] ID[[.]] NO: 9 MMTVLKVRKR; and

SEQ[[.]] ID[[.]] NO: 10 MMTVLKVRK.

Please replace the paragraph beginning at page 25, line 13 as with the following amended paragraph:

SEQ ID [[No.]]NO: 73 Mouse S3 (333 amino acids)

Please replace the paragraph beginning at page 25, line 21 as with the following amended paragraph:

SEQ ID [[No.]]NO: 74 Human S3 (242 amino acids)

Please replace the paragraph beginning at page 26, line 5 as with the following amended paragraph:

SEQ ID [[No.]]NO: 75 Mouse S7 (221 amino acids)

Please replace the paragraph beginning at page 26, line 10 as with the following amended paragraph:

SEQ ID [[No.]]NO: 76 Human S7 (221 amino acids)

Please replace the paragraph beginning at page 27, line 3 as with the following amended paragraph:

SEQ ID [[No.]]NO: 77 Mouse V2

Please replace the paragraph beginning at page 27, line 13 as with the following amended paragraph:

SEQ ID [[NO.]]NO: 79 V2 – mouse

Please replace the paragraph beginning at page 28, line 1 as with the following amended paragraph:

SEQ ID NO: 78 Human V2

Please replace the paragraph beginning at page 28, line 12 as with the following amended paragraph:

SEQ ID [No 79]NO: 83 Human V3

Please replace the paragraph beginning at page 28, line 20 as with the following amended paragraph:

SEQ ID [[No]]NO: 80 V3 – mouse

Please replace the paragraph beginning at page 39, line 11 as with the following amended paragraph:

The plasmids used herein for expression of a desired protein or polypeptide include a promoter designed for expression of the proteins in a bacterial host. Suitable promoters are widely available and are well known in the art. Inducible or constitutive promoters are preferred. Such promoters for expression in bacteria include promoters from the T7 phage and other phages, such as T3, T5, and SP6, and the trp, lpp, and lac operons. Hybrid promoters (*see*, U.S. Patent No. 4,551,433), such as tac and trc, may also be used. Promoters for expression in eukaryotic cells include the P10 or polyhedron gene promoter of baculovirus/insect cell expression systems (*see, e.g.*, U.S. Patent Nos. 5,243,041, 5,242,687, 5,266,317, 4,745,051, and 5,169,784), mouse mammary tumor virus long terminal repeat (MMTV LTR), rous sarcoma virus long terminal repeat (RSV LTR), SV40, metallothionein promoter (*see, e.g.*, U.S. Patent No. 4,870,009) and other inducible promoters. For expression of the proteins, a promoter is inserted in operative linkage with the coding region of the desired protein or polypeptide.

Please replace the paragraph beginning at page 44, line 16 as with the following amended paragraph:

Within one embodiment, the polypeptide BX7B (SEQ ID NO:28) comprises a polypeptide wherein B is a basic amino acid and X7 is a sequence of about seven residues selected from any amino acid other than an acidic amino acid, wherein the peptide forms an alpha helix and each occurrence of B is oriented on the same side of the alpha helix, and with the proviso that the peptide does not consist of the sequences BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPVVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPVVR, or HREARSGKYK (SEQ ID [[Nos.]]NOs: 29-44 respectively).

Please replace the paragraph beginning at page 44, line 25 as with the following amended paragraph:

In one embodiment, the polypeptide can be (a) a first peptide comprised of a hyaluronic acid-binding domain; (b) a hyaladherin polypeptide; (c) a second peptide comprised of a domain from a hyaladherin polypeptide; (d) a hyaladherin-binding polypeptide; (e) a third peptide comprised of a hyaladherin binding domain. Also provided are antibodies which binds to a peptide or polypeptide of (a)-(d); and/or vectors (e.g., gene delivery vectors described below) that expresses a gene encoding a polypeptide as described above or herein. In a particular embodiment, peptides are provided comprised of a sequence selected from the group consisting of SEQ[[.]] ID NO: 1-20. In another embodiment, a hyaladherin-binding polypeptide comprised of SEQ[[.]] ID NO: 21.

Please replace the paragraph beginning at page 45, line 8 as with the following amended paragraph:

Within particularly preferred embodiments of the invention, the compound is an antibody. Representative examples of antibodies suitable for use within the present invention

include antibodies to domain D1 of RHAMM amino acids 1-164 of human RHAMM (including for example: sequences recognizing the murine D1 sequence, aa. 97-111 – QERGTQDKRIQDME (SEQ ID NO:21); and sequences recognizing human RHAMM, aa 151-164 – LKSKFSENGNQKNL (SEQ ID NO:18)); antibodies to domain D2 of RHAMM - the “leucine zipper” domain of human RHAMM from aa 195-222; antibodies which recognize the domain D3 –the TAM domains of RHAMM (aa 219-240 of the human RHAMM sequence, including antibodies which recognize the sequence VSIEKEKIDEK (SEQ ID NO:49)); domain D4 (repeat or “R” domain – aa 442-546 for mouse, and aa 442-463 for human) and domain D5 (HA binding domain, including two domains: aa 721-730 and aa 742-752 for mouse; aa 635-645 and aa 657-666 for human). In other embodiments, antibodies are provided which bind to a polypeptide comprised of SEQ[[.]] ID NO: 11-20.

Please replace the paragraph beginning at page 45, line 22 as with the following amended paragraph:

As utilized herein, reference may be made to the human sequence of RHAMM for identification of the domains. However, the domains can be identified and specific antibodies generated for other species, such as, for example, mouse. Figure 50 (SEQ ID [[Nos.]]Nos: 47 and 48) provides the amino acid sequence of human and mouse RHAMM (see PCT publication No. WO 97/38098 and Genbank Accession Nos. AAC52049 & Q00547). As utilized herein, it should be understood that antibodies “bind” to the above sequence if they do so with a K_d of at least 10^{-7} M (moles/liter) (see “antibodies” above).

Please replace the paragraph beginning at page 52, line 5 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating inflammatory neurological diseases such as Parkinsons, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as

polypeptides comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID [no. 71]NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 [[kd]]kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 54, line 5 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating Alzheimer disease, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 [[kd]]kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 56, line 20 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating arthritis (e.g., rheumatoid arthritis or osteoarthritis), comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an

antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 58, line 26 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating osteoporosis, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 59, line 24 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating multiple sclerosis, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene

delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 60, line 11 as with the following amended paragraph:

Within another embodiment methods are provided for treating multiple sclerosis, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 71,73 to 77 which binds HA; and (b) an antibody to SEQ ID ~~No. 71~~NO: 81,73 to 77. The dosage range for these peptides varies from 0.001mg/kg to 50mg/kg.

Please replace the paragraph beginning at page 61, line 13 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating inflammatory dermatosis (e.g., psoriasis), comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID No. 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 63, line 2 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating inflammatory bowel disease, comprising administering to a patient a compound selected from the group

consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 74~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 64, line 6 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating the above described treating diseases (e.g., lupus, diabetes mellitus, or, kidney fibrosis), comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 74~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[No.]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 67, line 1 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating the aforementioned diseases associated with wounds / wound healing, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino

acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]NO: 70~~), P-16 (Sequence ID ~~[[No.]]NO: 26~~); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]NO: 72~~); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 68, line 16 as with the following amended paragraph:

Thus, within one embodiment methods are provided for inflammatory / proliferative diseases associated with surgical procedures or intervention (e.g., restenosis, stenosis, medical implants and the like), comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]NO: 70~~), P-16 (Sequence ID ~~[[No.]]NO: 26~~); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]NO: 72~~); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 70, line 1 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating the above-noted atherosclerotic diseases, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides

comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 [[kd]]kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 71, line 11 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating patients undergoing tissue or cell transplation, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such such as polypeptides comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 [[kd]]kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 74, line 4 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating cancer and other metaseses, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID [[No.]]NO: 70), P-16 (Sequence ID [[No.]]NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID [[No.]]NO: 72); (b) an antibody which binds one of

domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 75, line 8 as with the following amended paragraph:

Thus, within one embodiment methods are provided for treating chronic and acute distress syndromes, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated.

Please replace the paragraph beginning at page 76, line 18 as with the following amended paragraph:

Within one embodiment methods are provided for treating or preventing diabetes mellitus, comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence BX7B (SEQ ID NO:28) which binds HA; phage display selected peptides that bind HA such as polypeptides comprising P-15 (Sequence ID ~~[[No.]]~~NO: 70), P-16 (Sequence ID ~~[[No.]]~~NO: 26); P-32 (Sequence ID ~~no. 71~~NO: 81); and GAHWQFNALTVR (Sequence ID ~~[[No.]]~~NO: 72); (b) an antibody which binds one of domains D1, D2, D3, D4, or D5 of RHAMM; (c) a peptide of less than 95 kD or 73 ~~[[kd]]~~kD, comprising all or a portion of domains D1, D2, D3, D4, or, D5 of RHAMM; and (d) a gene delivery vector

which expresses antisense RHAMM, or, delivers and expresses any one of (a), (b), or (c), such that the disease is treated. Within certain embodiments of the invention, the compounds described herein may be administered before, during, or subsequent to islet-cell transplantation. Within other related embodiments, the above-described compounds may be utilized to treat related diseases, including for example, obesity.

Please replace the paragraph beginning at page 77, line 8 as with the following amended paragraph:

Within another embodiment methods are provided for diabetes comprising administering to a patient a compound selected from the group consisting of (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: ~~[[71]]~~81, 73 to 77 which binds HA; and (b) an antibody to SEQ ID No. ~~71~~NO: 81, 73 to 77. The dosage range for these peptides varies from 0.001mg/kg to 50mg/kg.

Please replace the paragraph beginning at page 80, line 5 as with the following amended paragraph:

In disease or injury, mediators such as cytokines, growth factors and genetic mutations activate a myriad of responses leading in increased expression of AP-1 dependent genes (Figure 1). These genes are required for cell proliferation, migration, inflammation, tissue destruction and abnormal tissue remodeling. The activation of the AP-1 pathway occurs through the activation of the mitogen activated protein (MAP) kinase. The present invention discloses that in normal cells the activation of the AP-1 pathway by cytokines and other mediators is restricted and thus genes involved in disease cannot be induced significantly. Further this restriction is a result of the lack of extracellular signal-regulated kinase-1 (ERK-1) activation in normal cells (Figure 2). Normal cells must undergo a series of transitional stages to form a diseased state cell containing focal adhesions and is then responsive to inflammatory mediators. Transition stage cells provided by the present invention constitutively form podosomes and are unable to establish focal adhesions. Sustained formation of podosomes leads to the formation of

focal adhesions and results in a diseased state (Figure 3). The present invention further discloses a requirement for focal adhesions for maximal activation of *erk* kinase in response to growth factors and cytokines. Cellular response-to-injury processes including growth factor mediated responses which lead to cellular proliferation, migration, production of destructive enzymes and abnormal tissue remodeling are characterized by a maximal activation of the *erk* kinase signaling pathway. To demonstrate that this response requires the presence of focal adhesions, the response to IL-1 induction of *erk* kinase signaling was measured in cells grown under conditions permitting or preventing the formation of focal adhesions.

Please replace the paragraph beginning at page 84, line 19 as with the following amended paragraph:

The amount of ERK2 and phosphorylated mitogen activated protein kinase (MAPK) was detected from the total extracts by western blot using an ECL chemiluminescence system. In brief, lysates of 25 µg total protein were resolved by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto nitrocellulose membrane (BioBlot, Costar) using Trans-Blot® Semi-Dry Electrophoretic Transfer Cell (BioRad) with a transfer-blotting buffer containing 20 mM Tris, 150 mM glycine, 0.01% SDS and 20% methanol. The filters were blocked for non-fat skim milk in Tris-buffered saline Tween-20 (TBS-T) (20 mM Tris, pH 7.5, 150 mM NaCl and 0.1% Tween 20) at 4°C overnight. The membranes were then probed with phospho-specific anti-p44/p42 MAP kinase antibody (New England BioLabs, Inc.) by incubation at room temperature for 1.5 h. After washing three times with TBS-T for 30 min, blots were incubated with horseradish peroxidase conjugated anti-rabbit antibodies (NEB) for 1 h. The filters were washed three times for 30 min and visualized on X-ray film using the chemiluminescence-detection method (NEB).

Please replace the paragraph beginning at page 89, line 1 as with the following amended paragraph:

Figure 10 shows a phosphoprotein activity analysis that directly illustrates that cells that overexpress RHAMM have elevated *erk* activation of MAP kinases but that this activation is restricted relative to the level of activity observed in normal cells induced by a growth factor platelet-derived growth factor (PDGF). The Figure shows both phosphorylation of *erk* molecules and *erk2* dependent phosphorylation of MBP molecules.

Please replace the paragraph beginning at page 89, line 6 as with the following amended paragraph:

Briefly, cells were grown in DMEM with 10% FBS, and cells were starved for 6 h in the medium without serum. Cells were then stimulated with PDGF (25 ng/ml) for 30 and 60 min. Cell monolayers were washed three times with PBS and total cellular extracts were prepared in a buffer containing 25 mM Hepes, pH 7.7, 100 mM NaCl, 2 mM MgCl₂, 0.2 mM EDTA, 0.5% Triton X-100, 0.5 mM DTT, 20 mM β-glycerophosphate, 0.1 mM sodium orthovanadate, 0.5 μg/ml leupeptin, 100 μg/ml PMSF. Cellular lysates of 100 μg total protein were incubated with anti-ERK2 antibody conjugated agarose (ERK(C-14), Santa Cruz Biotech., Inc.), immuno-complexes were washed twice with the above lysis buffer and twice by kinase buffer (20 mM Hepes, pH 7.7, 10 mM MgCl₂, 2 mM MnCl₂, 2 mM DTT and 25 μM ATP). Extracellular signal-regulated kinase-2 (ERK2) activity was determined by *in vitro* kinase assay using 2 μg substrate MBP and 1 μCi [γ-³²P] ATP in 20 μl of kinase buffer. After incubation at 30°C for 20 min, the reactions were terminated with Laemmli buffer, and proteins were separated by SDS-PAGE, gels were dried and autoradiography.

Please replace the paragraph beginning at page 90, line 14 as with the following amended paragraph:

Figure 11B shows a Northern analysis of tumor necrosis factor-alpha (TNF-α) induction of *c-fos* expression in 10T1/2 and LR21 cell lines. Cells were grown in DMEM with 10% FBS and starved for 6 h in the medium without serum. Cells were then stimulated with TNF-α (30 ng/ml) for 30 min and 60 min. Total RNAs were extracted and hybridized as

described above. The level of *c-fos* was measured by hybridization with a rat *c-fos* cDNA. Again it can be seen that the expression of *c-fos* in response to an injury response growth factor *i.e.*, TNF- α , is restricted in LR21 cells.

Please replace the paragraph beginning at page 94, line 3 as with the following amended paragraph:

Figure 21 shows that RHAMM binds to fibronectin but is blocked by antibody to exon 3 indicating that exon 3 contains a fibronectin binding domain. Figure 21 further illustrates that RHAMM binds to the CS-1 fragment of fibronectin and not to the RGDS sequence which was previously considered to be a critical sequence for fibronectin signaling of matrix protein degradation. Panel A shows that RHAMM binds to fibronectin as detected by an enzyme-linked immunosorbent assay (ELISA). Panel B shows that exon 3 of RHAMM binds to fibronectin but not through the RGDS region but rather through the CS-1 region. Panel C shows that peptides mimicking exon 3 are able to block the binding of intact RHAMM to fibronectin, providing a rationale for why peptides block cell locomotion and podosome formation.

Please replace the paragraph beginning at page 102, line 19 as with the following amended paragraph:

To quantify the effect of RHAMM sequence ~~(423-432-AA)~~(amino acid residues 423-432; 423-432AA) to alter velocity of cell locomotion human fibroblasts were seeded on T-12.5 fibronectin coated flasks using α -MEM supplemented with glucose and 10% FBS. 2.5×10^4 cells were seeded and cells incubated for 4 hrs at 37°C. After incubation time cells were treated with increasing concentrations of RHAMM sequence peptide (423-432 AA, 0.1, 1.0, 5.0, 10 and 50 ng/ml) and cell locomotion was monitored over the period of 16 hrs on a 37 °C using 10X modulation objective (Zeiss, Germany) attached to a Zeiss Axiovert 100 inverted microscope equipped with Hoffman Modulation contrast optical filters (Greenvale, NY). Cell images were captured with a CCD video camera module attached to a Hamamatsu CCD camera controller. Motility was assessed using Northern Exposure 2.9 image analysis software (Empix

Imaging, Mississauga, Ontario). Nuclear displacement of 7 – 10 cells was measured and data were subjected to statistical analysis. Statistically significant ($P < 0.05$) differences between means were assessed by the unpaired Student's T-test method, performed using Microsoft Excel "97 software.

Please replace the paragraph beginning at page 105, line 6 as with the following amended paragraph:

Briefly, mouse normal and RHAMM knockout fibroblasts are plated in DMEM medium and starved overnight. Medium was changed and two different concentrations of PDGF added. After 10 min cells were lysed in radioimmunoprecipitation (RIPA) buffer. Western blot analysis was done and proteins separated by SDS-PAGE. Bands were visualized by phospho-specific erk antibody. Subsequently, blot was stripped and reprobed with erk antibody.

Please replace the paragraph beginning at page 110, line 18 as with the following amended paragraph:

In order to investigate if there is any RHAMM expressed in the synovium tissue of RA patients, immunohistochemistry was done. Briefly, pannus formed from synovium tissue was isolated and embedded in wax. Three microns tissue sections were obtained and slides were heated on 58°C for 30 min. To deparafinize slides the following procedure was done: tissue sections were washed in xylene three times each four minutes. After washing in xylene, slides were washed in 100% ethanol two times each three minutes. Additionally sections were washed in 96% ethanol the same amount of time. Slides were then incubated in dH₂O two times each three minutes and once in PBS. Tissue on the slides was then marked with barrier-pen. The activity of endogenous peroxidase was blocked with 0.3% of hydrogen peroxide for 10 min. Slides were washed with dH₂O two times each 3 minutes and with PBS two times each 5 minutes. Unspecific binding was blocked with 1% bovine serum albumin (BSA) in PBS at 37°C for 30 minutes. Different dilutions of RHAMMv4 and RHAMM R3.8 antibodies were made: 1:100, 1:50, 1:25) in 1% BSA-PBS and incubated with tissue samples overnight at +4°C. Two

tissue sections served as controls and they were incubated with either rabbit IgG (at the same dilution as the antibodies) or with vehicle which was 1%BSA PBS, without primary antibody. After incubation with primary antibodies, slides were washed with PBS three times, 10 minutes each. Consequently, biotinylated antirabbit IgG was added and slides kept at room temperature for 1 hour (dil.1:200 in BSA-PBS). Slides were again washed with PBS three times each 10 minutes. Additionally, Avidin-biotin complex (ABC) reagent was premixed and incubated with slides at room temperature for one hour. Slides were washed with PBS three times each time 5 minutes. After washing, 3,3'-diaminobenzidine (DAB) solution was premixed and incubated with slides for 5 minutes at room temperature. Samples were washed with dH₂O three times each time 5 minutes and counterstained with hematoxyline for 1-2 minutes. Samples were washed with regular water and dehydrated. For dehydration similar procedure was done as for deparafinization only this time steps were done backwards. Slides were mounted and left to dry overnight.

Please replace the paragraph beginning at page 111, line 20 as with the following amended paragraph:

Results are shown in Figure 38. Briefly, synovium tissue isolated from joints of a rheumatoid arthritis (RA) patient was positively stained (brawn staining) with RHAMM exon4 (pictures A and B) and RHAMM R3.8 (pictures C and D). Areas of synovial lining cells are enriched in RHAMM staining which are most likely macrophage cell type, although other cell types in the RA synovium also express RHAMM (pictures A, B, C and D). Controls BSA (picture E) and rabbit IgG (picture F) are unstained.

Please replace the paragraph beginning at page 115, line 4 as with the following amended paragraph:

Frozen wound samples (50-100 mg tissue) were homogenized in 1 ml of Trizol reagent and RNA was isolated according to standard Trizol Reagent Protocol. For the synthesis of oligo-dT-primed cDNA, 2µg of total RNA, 1 µg of oligo(dT) primers and Moloney Murine

Leukemia Virus Reverse Transcriptase (Gibco Brl # 28025-013) were used. Following 1 h incubation at 37°C, the reaction was stopped by heating samples at 95°C for 5 min and 2 µl of reverse transcriptase (RT) reaction mixture was used for polymerase chain reaction (PCR). PCR amplification was performed with platinum Taq DNA polymerase (Gibco BRL #10966-018) and specific primers for collagen I and III were used: 5' CGA TGT CGC TAT CCA GCT GA (SEQ ID NO:52) for collagen I and the following primer 5' ATC AGT CAG CCA TCT ACC ACC (SEQ ID NO:53) was used for collagen type III. Thermal cycles for collagen type I and III were as follows: denaturation at 94°C, annealing at 60°C and polymerization at 72°C for 20 cycles. In addition, a set of primers of a common housekeeping gene B-actin, were run in parallel on 1.5% agarose gel as a loading standard.

Please replace the paragraph beginning at page 127, line 24 as with the following amended paragraph:

In addition to specific peptides such as those described in SEQ. ID NOS: 1-10 that represent hyaladherins which bind to hyalauronic acid, a variant of additional polypeptides may be identified, generated and tested for use within the methods described herein. All such binding motifs are characterized by the presence of general amino acid motifs including staggered basic residues. These motifs can be more generally described as BX7B (SEQ ID NO:28) where B is any basic amino acid and X7 is any amino acid sequence of about seven residues but usually including at least one hydrophobic amino acids or an additional basic amino acid. Most importantly however, none of the intervening X amino acids should be acidic, as acidic amino acids appear to interfere with binding to hyaluronan, a negatively charged polymer. Peptides which are specifically excluded from this motif include: BBXXBBBXXBB, KQKIKHVVKLK, KLKSQLVKRK, RYPISRPRKR, KNGRYSISR, RDGTRYVQKGEYR, RRRCGQKKK, RGTRSGSTR, RRRKKIQGRSKR, RKSYGKYQGR, KVGKSPPVR, KTFGKMKPR, RIKWSRVSK, KRTMRPTRR, KVGKSPPVR, or HREARSGKYK (SEQ ID [[Nos.]]NOS: 29-44 respectively). These excluded peptides do not bind HA with the same high affinity as peptides of the present invention which require are peptides that form an alpha helix.

All motifs that bind to hyaluronan also preferably form strong alpha helices as predicted in secondary structure protein analysis programs which further show that hyaluronan binding motifs contain at least two basic amino acids aggregating along one plane of the helix.

Please replace the paragraph beginning at page 131, line 23 as with the following amended paragraph:

Serum and tissue levels of hyaluronic acid (HA) are valuable diagnostic markers of arthritis and neoplasia. Thus, levels of HA in the serum are currently used to follow the course of osteoarthritis response to steroid therapy. Further, HA accumulation within colorectal and breast cancers is prognostic of a poor outcome. Because HA levels are enhanced following most forms of tissue injury, other conditions including restenosis, MS, Alzheimer's, stroke, myocardial infarction, sports injuries, burns and other inflammatory diseases would benefit from methods of detecting HA. In addition, HA increase in plasma is associated with a variety of other diseases, particularly rheumatoid arthritis and in tumors such as mesotheliomas and Wilm's tumors. Therefore testing of HA levels in serum or in biopsy tissue will be useful, alone or in combination with other disease markers for determination of a variety of disease conditions.

Please replace the paragraph beginning at page 136, line 17 as with the following amended paragraph:

Thus, RHAMM is preferentially expressed in more motile/invasive and metastatic carcinoma of the prostate (CaP) cells. Blocking RHAMM function significantly and preferentially reduces motility, invasion, and MMP activity in highly metastatic CaP cells.

Please replace the paragraph beginning at page 138, line 15 as with the following amended paragraph:

These results indicate that RHAMM and its major ligand HA associate functionally with autoimmune insulinitis leading to insulin-dependent diabetes mellitus (IDDM), and that by using specific RHAMM peptides they can serve as potential therapeutic targets.